REMARKS

Status of the Claims

Claims 2-4, 38 and 78-96 are pending are shown in the Response filed August 30, 2005. Claim 38 is under active examination.

By amendment herein, withdrawn claims 2-4 and examined claim 38 have been amended to make explicit what was previously implicit in the recitation of an expression cassette, namely that the claimed polynucleotides encode an immunogenic Env polypeptide. Support of the amendments can be found throughout the specification as filed, for example in Section 2.4. Thus, claims 2-4, 38 and 78-96 are pending as shown above and claim 38 is under active consideration.

Restriction Requirement

As correctly noted by the Examiner the Restriction Requirement was petitioned and deemed proper by the Group Director. (Final Office Action, page 1). Nonetheless, Applicants reiterate that the basis for the Restriction, namely that the sequences have no "common core," is inconsistent with the evidence of record. As shown in the alignment of SEQ ID NOs:120 and 121 submitted with the Response to Restriction Requirement and the alignment of all of the sequences recited in claim 38 along with SEQ ID NOs: 46 and 47 (claims 2 and 3, depicting common regions of Env) submitted with the previous response. This evidence establishes that there is, in fact, a high degree of homology between the sequences of all the pending claims. As such, searching the art for the full-length of any of these sequences would necessarily reveal references relevant to all other sequences and, as such, it would <u>not</u> impart a serious burden on the Examiner to search them together.

In any event, Applicants are entitled to rejoinder of process claims 78-96 when the elected product claim 38 is found allowable.

Applicants again expressly reserve their right under 35 USC §121 to file one or more divisional applications directed to the nonelected subject matter during the pendency of this application.

IDS

In the Final Office Action, the Examiner first indicated that the IDS had been placed in the file and the information therein had "been considered." (Final Office Action, page 1). However, in the following sentence, it was noted that the IDS has not been considered on the grounds that were an excessive number of references and, as such, a statement regarding the relevance of each reference was required. (Final Office Action, pages 1-2). The returned 1449 forms also indicated that the references had not been considered.

Applicants submit that all the references must be considered because a statement of relevance of each reference is NOT required for references provided in English (37 C.F.R. 1.98(a)(3)(i)):

> A concise explanation of the relevance ...of each patent, publication or other information listed **that is not in the English language**. The concise explanation may be either separate from applicant's specification or incorporated therein.

Therefore, Applicants are not required to provide a concise application for any of the references cited in the IDS. Certainly, the Examiner must consider the IDS filed June 28, 2005, which contains only 8 references.

In sum, the documents submitted in the Information Disclosure Statements in this application should all be considered on their merits.

Inventorship

Applicants note with appreciation that the change to inventorship has been entered.

35 U.S.C. § 112, 1st Paragraph, Written Description

Claim 38 was again rejected under 35 U.S.C § 112, first paragraph as allegedly not described by the specification as filed. (Final Office Action, pages 2-6). In particular, on pages 2 to 5, the Examiner summarizes the holdings in various written description cases. In the last two paragraphs of the rejection, the Examiner asserts that (1) the claims do not limit the polynucleotide sequence to any particular length; (2) there is no limitation as to where the variant

nucleotides may occur; (3) a "core structure" is not described; and (4) the disclosure fails to provide any "significant structural/functional guidance identifying potential regions that can tolerate such a large number of changes without abrogating the various activities of Env (i.e., virion-receptor binding)."

Applicants again traverse the rejection and supporting remarks.

1. The Claims Limit the Length of the Polynucleotide Sequence

Contrary to the Examiner's statement, the claim amendments made in the previous response specifying that the claimed sequences have at least 90% sequence identity to the "full-length" of the reference sequence obviates the rejection.

Indeed, Applicants reiterate that each and every member of the claimed genus – be it 2 or 20,000 members in size – is **literally** described in the as-filed specification. Satisfaction of the written description requirement does not necessitate that each and every member of the claimed genus be set forth in the as-filed specification. Indeed, it is axiomatic that a patent specification "need not teach, and preferably omits, what is well known in the art." See, *Spectra-Physics, Inc. v. Coherent, Inc.* 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, there is no requirement to describe that which is well-known at the time of filing. Indeed, this has recently been reiterated by the Federal Circuit in *Capon v. Eshhar* 76 USPQ2d 1078 (CA FC 2005):

> It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 [190 USPQ 214] (CCPA 1976) ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. ...

In other words, a specification need not describe every polynucleotide permutation in order for an inventor to obtain a generic claim.

Nor does the written description requirement necessitate a showing that the skilled artisan can predict *a priori* each and every nucleotide sequence falling within the scope of the claims. Even if it did, Appellants have met this inasmuch as the as-filed specification contains

unambiguous **literal** description of the structure of any member of the claimed genus by reference to its sequence similarity to the full-length of a reference sequence.

Thus, not only is the genus not as broad as painted by the Examiner by virtue of the limitation requiring that 90% sequence homology be to the full-length reference sequence, it is clear that every member of the genus is described by the as-filed specification. On this basis alone, the rejection should be withdrawn.

2. The Claim Term "encodes an Immunogenic Env polypeptide" Cannot Be Read Out of the Claim

However, the instant claims are not directed to any sequence having 90% identity polypeptide. Rather, the claimed sequences must encode an immunogenic HIV Env polypeptide. In other words, the immunogenic response elicited by the encoded polypeptide is a response specific for HIV Env.

As clearly used throughout the specification, the term "immunogenic HIV polypeptide" refers only to HIV Env polypeptides elicit an immune response. *See, e.g.,* page 30, line 19 to page 32, line 4, wherein it is clearly noted that an immunogenic polypeptide is one which elicits a humoral and/or cellular immune response "to the antigenic molecule of interest," in this case a immune response to HIV Env. *See, also,* page 105, lines 17-20 of the as-filed specification, which clearly indicates that the HIV Env polypeptide is immunogenic and that the immunogenicity of the polypeptide can be increased, for example by deleting various regions.

In addition to the fact that the specification clearly teaches that the polypeptide encoded by the claimed sequences is an immunogenic HIV Env polypeptide, Appellants believe that the Examiner's reading of "immunogenic" out of the context with "HIV Env polypeptide" renders the claim meaningless and fails to comport with the knowledge of one of skill in the art in the field of HIV and molecular biology.

It was well known at the time of filing that a sequence encoding an HIV Env polypeptide would elicit an immune response specific for HIV Env. *See, e.g.,* U.S. Patent Nos. 5,846,546; 5,840,313; and 5,876,731, cited on page 3 of the specification and references A27, A26 and A32 of IDS filed June 4, 2003, respectively.

To assert that the term "immunogenic HIV Env polypeptide" does not limit the scope of the claims on the grounds that any polypeptide is immunogenic stretches the meaning of the claims beyond credulity. The skilled artisan would clearly recognize that an "immunogenic HIV Env polypeptide" is one that elicits an Env-specific immune response.

In light of the art, as exemplified by the references discussed above, the term "immunogenic HIV Env polypeptide" cannot be construed to encompass polypeptides that induce general, non-Env-specific immune responses. Indeed, the importance of construing claim language in light of the art was recently reaffirmed by the Federal Circuit, *en banc*, in *Phillips v. AWH*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005). Therein, the court, citing a number of previous decisions,[1] confirmed its precedent that claim terms are given their ordinary and customary meaning to a person of ordinary skill in the art at the effective filing date of the patent application (*Phillips v. AWH Corp.,* 75 USPQ2d 1321, 1326 (Fed. Cir. 2005)):

> We have made clear, moreover, that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.

At the time of filing, the skilled artisan was well aware at that date, an "immunogenic HIV Env polypeptide" would not include polypeptides that did not elicit Env-specific immune responses.

Thus, the meaning attributed to the term "immunogenic HIV Env polypeptide" by the Examiner is not the meaning of that term as set forth in the specification or the meaning of the term to one of skill in the relevant art. The claimed sequences encode polypeptides that elicit specific (HIV Env) immune responses and sequences that do not encode polypeptides that produce an HIV Env-specific immune response are not encompassed by the pending claims. In other words, the genus encompassed by the claims is nowhere near as broad as that painted by the Examiner. When the claims are properly construed, it is plain that they are drawn to a genus

[1] See, for example, *Vitronics Corp. v. Conceptronic, Inc.* 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Ferguson Beauregard/Logic Controls v. Mega Sys., LLC,* 350 F.3d 1327, 1338 (Fed. Cir. 2003) and *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004)

of nucleotide sequences encompasses only those nucleotide sequences that encode a polypeptide that elicits a humoral and/or cellular immune response specific for an HIV Env polypeptide.

3. Identification of "Core" Regions is NOT Required to Show Possession of the Claimed Molecules

As noted above, the Examiner has also alleged that adequate written description of a nucleotide sequence requires the specification describe "potential regions that can tolerate such a large number of changes without abrogating the various activities of Env (i.e., virion-receptor binding)." (Final Office Action, page 6).

However, the claims are not directed to sequences encoding polypeptides having "various activities" of Env. They are directed only to sequences encoding polypeptides that elicit an Env-specific immune response. The specific nature of the antigen's (HIV Env) immunogenicity is described throughout the specification as filed, for instance, on page 29, lines 23-26 and page 30, line 19 to page 32, line 9, for example, page 32, lines 4-7 wherein it is clearly noted that an immunogenic polypeptide is one which elicits a humoral and/or cellular immune response "to the antigenic molecule of interest," in this case a immune response to HIV Env.

At the time of filing (and indeed to this day), it was well known by the skilled artisan that the correlation between polypeptide structure (primary sequence or tertiary structure) and specific immunogenic function is not one-to-one. Production of an immune response to an antigen is routinely practiced in the absence of knowledge of a protein's primary or tertiary structure. *See, also,* pages 29-30 of the as-filed specification regarding epitopes.

A single epitope is not responsible for immunogenicity. One of skill in the art can routinely produce antibodies that specifically bind to a protein by immunizing an appropriate host with oligopeptide fragments of that protein. It is well known in the art that it is possible to produce antibodies to almost any part of an antigen, and is not especially difficult to obtain antibodies with specificity for a particular protein, as set forth in the claims. Furthermore, a specific cellular immune response is also routinely produced by immunization with antigen. The specification provides amply guidance for one of skill in the art to elicit an immune response (*i.e.*, humoral and/or cellular) with the recited polynucleotides encoding HIV Env polypeptides

that elicit an Env-specific immune response. *See*, specification, *e.g.*, at Examples 2-7; Section 2.4 starting on page 77; and page 31.

The one common holding in written description cases (including those summarized on pages 2-5 of the Final Office Action) is that the written description inquiry is fact-dependent. Accordingly, satisfaction of the written description requirement will depend on what is claimed. Claims drawn to molecules that function as enzymes may require description of a "core structure" responsible for enzymatic behavior. By contrast, the facts indicate that description of a "core structure" is not required (and, indeed, not possible) when the claims are drawn to molecules that encode polypeptides which elicit a specific immune response, as in the instant case. When properly considered on the facts, it is clear that satisfaction of the written description requirement in the pending case does not hinge on whether a "core region" is described.

In sum, the evidence of record clearly establishes identifying a "potential regions" associated with "various Env activities" is not required in order to evince possession of the claimed sequences (which encode polypeptides that elicit an immune response specific for an HIV Env polypeptide) and satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

4. Possession of the Claimed Genus Has Been Established

Additional evidence also establishes that, at the time of filing, Applicants were in possession of all members of the claimed genus. Description does not require exemplification. In fact, it is well settled that description of a single species can provide an adequate description, even for a broad genus. In particular, the PTO Guidelines, favorably commented on by the Federal Circuit in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1617 (Fed. Cir. 2003), include various Examples that establish that claims to a genus of sequences are properly described if (1) the DNA sequence is novel, (2) unobvious, (3) a specific activity is recited, and (4) assays are provided for determining variants having the recited activity. In particular, Examples 9 and 14 of the PTO Guidelines read, in part, as follows (underlining added):

Example 9: Hybridization

Specification: The specification discloses a single cDNA (SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification includes an example wherein the complement of SEQ ID NO:1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity. The hybridizing nucleic acids were not sequences. ... These sequences may or may not be the same as SEQ ID NO:1.

Claim: An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

Analysis: A review of the full content of the specification indicates that the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO:1 under highly stringent conditions and encodes a protein with a specific function. The art indicates that hybridization techniques using a known DNA as probe under highly stringent conditions were conventional in the art at the time of filing.

The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO:1 and must encode a protein with a specific activity.
The search of the prior art indicates that SEQ ID NO:1 is novel and unobvious.

There is a <u>single species disclosed</u> (a molecule consisting of SEQ ID NO:1) that is within the scope of the claimed genus.

Now turning to the <u>genus analysis</u>, a person of skill in the art would <u>not</u> expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization <u>conditions set forth in the claim yield structurally similar</u> DNAs. <u>Thus, a representative number of species is disclosed, since</u> highly stringent hybridization <u>conditions in combination</u> with the coding function of DNA and <u>the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention</u>.

Conclusion: The claimed invention is adequately described.

Example 14: Product-by-Function

Claim: A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→ B.

> **Analysis**: ... The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art. ....
>
> There is actual reduction to practice of a single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion**: The disclosure meets the requirements of 35 U.S.C. § 112, first paragraph as providing adequate written description for the claimed invention.

Examples 9 and 14 are highly instructive to the claims at issue and establish that the claimed genus is more than adequately described.

Indeed, as in Example 9, a review of the full content of the specification at issue indicates that the essential feature of the claimed invention is a sequence which encodes an immunogenic HIV Env polypeptide but which is unlike a wild type sequence. The art indicates that it was conventional at the time of filing to determine percent identity as between any sequences. Determining the polypeptide encoded by any given sequence was also conventional at the time of filing. In other words, the specification's clear description of the unconventional elements of the claimed subject matter is more than ample to indicate satisfaction of the written description requirement by evincing possession at the time of filing.

Moreover, as in Example 9, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because of the requirement in the claims that the sequences must exhibit both 90% identity to the reference sequence (analogous to stringent hybridization conditions of Example 9) and encode an immunogenic HIV Env polypeptide (analogous to encoding a protein that binds to a dopamine receptor and

stimulates adenylate cyclase activity in Example 9). Accordingly, a representative number of species is disclosed, since the identification of percent identity in combination with the function of encoding an immunogenic HIV Env polypeptide and the level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed invention at the time of filing.

Like Example 9, Example 14 of the PTO Guidelines, entitled "product-by-function," also illustrates a fact pattern that is highly instructive in the pending case. In this regard, the pending claims are analogous to the "product by function" claim presented in PTO Example 14 in that they all recite a reference structure, the particular mutations and include a functional limitation (catalytic activity in PTO Example 14 and encoding an immunogenic HIV Env polypeptide in the claims at issue).

Furthermore, as determined by Patent Office, procedures for determining percent identity and evaluating proteins encoded were utterly conventional in the art at the time of filing and described in the pending application.

Moreover, like Example 14, the disclosure in the as-filed specification of assays for determining variants having the recited functional activity must be considered in determining adequacy of description. Here, the as-filed specification discloses multiple assays (ELISAs, Western blotting, CTL assays, etc.) for determining whether the claimed functional activity – eliciting an Env-specific immune response. *See, e.g.,* Section 2.1.2 starting on page 51, Examples of the specification. Accordingly, as in Example 14, because of the presence of an assay for identifying all variants having the specified activity, Applicants have demonstrated possession of the claimed genus of molecules.

Therefore, actual reduction to practice of a single disclosed species is more than sufficient to satisfy the written description requirement in the case at hand because, as in PTO Examples 9 and 14, sequences falling within the claimed genus must have the recited structure and function. The issue is **not** the size of the genus, but what the specification conveys to the skilled artisan. The skilled artisan, having followed the teaching of the specification, would have no doubts that (1) Applicants were in possession of the claimed subject matter and that (2) Applicants' as-filed specification teaches how to make and use the claimed sequences.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Please direct all further written communications regarding this application to:

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